Abstract

The work presented is this thesis is divided into two chapters. The first chapter is based on the synthesis and applications of ion-tagged proline based organocatalysts, particularly, novel proline-histidine dipeptide derivatives and various asymmetric transformations carried out by them. The second chapter deals with the applications of arginine and proline as catalysts for effecting carbon-carbon bond forming transformations towards the synthesis of important compounds and intermediates.

Chapter 1:

The chapter is divided into four sections. The first section includes a concise introduction towards ion-tagged proline based compounds as organocatalysts and their applications in various asymmetric carbon-carbon bond forming reactions. The second section involves the synthesis of proline-histidine dipeptide derivatives as ion-tagged catalysts and studies on their efficiency in the direct asymmetric aldol reaction. Subsequently, the third section presents the synthesis of oxa-bicyclo[2.2.2]octanones via an aldol-oxa-Michael reaction using proline-histidine dipeptide derivatives. The last section describes the enantioselective construction of tetrahydroxanthenones by an organocatalytic oxa-Michael-aldol approach using the same proline-histidine dipeptide derivatives.

Section 1A: An Overview of Ion-tagged Organocatalysts in Asymmetric Synthesis

In the recent years, ionic liquids have appeared as promising candidates to facilitate the recovery and reuse of precious organocatalysts. Further advancement in the area provided the “non-solvent applications” of ionic liquids, better known as “ion-tagged organocatalysts” in which the ionic liquid moiety is covalently attached to the organocatalyst. These ion-tagged organocatalysts provided a much superior isolation of products and recovery of organocatalyst. The section sheds light on the proline and proline based ion-tagged catalysts reported in the past decade and various organic asymmetric transformations carried out by them.

Section 1B: Proline-histidine dipeptide derived ion-tagged catalysts for the direct asymmetric aldol reaction

This section describes our efforts towards the synthesis of proline-histidine dipeptide derived ion-tagged organocatalysts and their application in the direct asymmetric aldol reaction. The aldol reaction of ketones and aromatic aldehydes were carried out by using the above catalyst and acid additives under solvent free conditions
in the presence of water. In result, the ion-tagged catalysts exhibited high activity and also provided excellent stereocontrol in the reaction (Scheme 1).

**Scheme 1:** Direct asymmetric aldol reaction catalyzed by proline-hitidine dipeptide derived ion-tagged catalysts

**Section 1C: Studies towards the synthesis of oxabicyclo[2.2.2]octanone compounds using a proline-hitidine dipeptide derived catalyst**

Bridged bicyclic skeletons, in particular, aza- and oxa-heteroatom containing bicyclo[2.2.2]octanones are ubiquitous structures in biologically active compounds. The chapter reveals the first aldol-oxa-Michael cascade approach (oxa-Diels-Alder type reaction) for the synthesis of oxa-bicyclo[2.2.2]octanones. These bicyclooxa-bridged compounds were formed exclusively as the exo isomer in good to moderate yields in the reaction of 2-cyclohexenone with aryl aldehydes catalysed by a proline-histidine dipeptide derivative (Scheme 2).

**Scheme 2:** Synthesis of oxa-bicyclo[2.2.2]octanones via domino aldol-Michael addition reaction using a proline-histidine dipeptide derivative

**Section 1D: Enantioselective synthesis of tetrahydroxanthenones via oxa-Michael-aldol reaction of salicylic aldehydes and 2-cyclohexenone using proline-histidine dipeptide derived catalysts**

The tricyclic tetrahydroxanthenone core is the most common and important motif in the family of xanthones and is used as a versatile intermediate for further
transformations towards the synthesis of bioactive natural products. Till date, only few reports are associated with the asymmetric synthesis of tetrahydroxanthones. This section describes our efforts towards the enantioselective synthesis of these tetrahydroxanthones by using ion-tagged proline-histidine dipeptide derivatives via an oxa-Michael-aldol cascade cyclisation sequence. The reaction of various salicylaldehydes with 2-cyclohexenone catalysed by the dipeptide in combination with a Bronsted acid additive in water provided the desired tetrahydroxanthones in good yields and good to excellent enantioselectivities (Scheme 3).

Scheme 3: Synthesis of tetrahydroxanthones by an oxa-Michael-aldol approach using ion-tagged proline-histidine dipeptide derivative as catalyst

Chapter 2:

The chapter is divided into three sections. The first section provides a detailed account on reports associated with various organic transformations catalyzed by arginine. The second section is focused on the switchable reactivity of methyl vinyl ketone, which delivered different products in reactions with aromatic aldehydes mediated by arginine and proline. The third section presents the results obtained from our efforts on the arginine mediated aldol addition of methyl vinyl ketone to isatins.

Section 2A: Arginines as catalysts in organic synthesis – an account

The literature covered in this chapter is focused on reports associated with the use of amidine and guanidine based compounds as organocatalysts for various organic transformations. Arginine, a naturally occurring inexpensive amino acid that bears the guanidine moiety on its side-chain, provides vast opportunities for the researchers to use it as a catalyst. Thus, the chapter also covered reports regarding the use of arginine as a bifunctional catalyst, wherein the guanidine moiety provided a site for similar H-bonding activation. The literature report provides a pointer to the possible avenues for the development of promising arginine derived catalysts for various reactions in future and also for developing newer arginine catalysed transformations.
Section 2B: A study on the amino acid based switchable reactivity of methyl vinyl ketone towards aldehydes

This section is divided into two sub-sections and focuses on the studies of an interesting contrast to the reactivity of methyl vinyl ketone with two different amino acids – proline and arginine – under nearly identical conditions. It was observed that with proline, the reaction of methyl vinyl ketone and aromatic aldehydes delivered the Baylis-Hillman adduct exclusively, whereas arginine provided exclusive formation of the aldol adduct (Scheme 4).

![Scheme 4: Switchable reactivity of methyl vinyl ketone with different amino acids](image)

Section 2B-I: Proline mediated Morita-Baylis-Hillman reaction of methyl vinyl ketone under solvent-free conditions

A proline-mediated Baylis–Hillman reaction of methyl vinyl ketone with aromatic aldehydes has been carried out without using any co-catalyst, under solvent-free conditions. The reaction works efficiently at 60 °C in the presence of a small amount of water to afford the Baylis–Hillman adducts in very good yields over 8–48 h. The absence of a co-catalyst suggests that proline plays a role in the proton transfer step of the reaction, in addition to its proposed involvement in the iminium ion formation and conjugate addition. This would, in principle, imply that proline acts as a trifunctional catalyst in the reaction, and mechanistic studies to gain a deeper understanding of this aspect should provide further insights in the future (Scheme 5).

![Scheme 5: Baylis-Hillman reaction between methyl vinyl ketone and various aromatic aldehydes using proline](image)
Section 2B-II: Arginine mediated aldol addition of methyl vinyl ketone to aromatic aldehydes in water

An aldolisation protocol for methyl vinyl ketone has been developed using an arginine mediated reaction in water. The reaction worked efficiently at 40 °C providing moderate to good yields of the aldol adducts (Scheme 6). The work assumes more importance considering the reportedly unstable nature of the products and their potential applications in natural product synthesis.

Scheme 6: Aldol reaction between methyl vinyl ketone and various aromatic aldehydes using arginine

Section 2C: Arginine catalyzed aldol addition of methyl vinyl ketone to isatins: rapid access to 3-alkyl-3-hydroxyindolin-2-ones

The first instance of an aldol addition between methyl vinyl ketone and isatins has been achieved using an arginine catalyzed protocol in water. The reaction progressed rapidly at room temperature to afford the corresponding 3-substituted-3-hydroxyindolin-2-ones in excellent yields. A further transformation of the aldol adduct was also carried out to access an interesting spirooxindole-pyranone skeleton in reasonable yield (Scheme 7). The method proved versatile, as exhibited by efficient aldolisations of other ketones also.

Scheme 7: Aldol between methyl vinyl ketone and isatins using arginine and transformation of the aldol adduct to aspirooxindole-pyranone